associated antigen" with the term "tumor antigen", even though Applicants believe that these terms are used interchangeably in the art. Applicants have amended claims 20-22 to simply insert a comma before the word "wherein". A marked up version of the claims amended herein, with deletions and additions indicated by brackets and underlining, respectively, is attached hereto as Exhibit A. Applicants respectfully assert that the amendments to the claims do not narrow the scope of the claims and do not constitute new matter. The amendments to the claims are fully supported by the specification (see, *e.g.*, p. 7, lines 22-25, p. 8, line 3, and p. 22 lines 17-22 of the specification).

The amendments and remarks herein narrow the issues on appeal and are designed to place the application into condition for allowance. As such, Applicants respectfully request that the amendments and remarks made herein be entered into the file and be fully considered.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-5, 20-22, 28 and 29 are rejected under 35 U.S.C § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 1-5, 20-22, 28 and 29 are also rejected under 35 U.S.C § 112, first paragraph, as allegedly not enabled by the specification. The Examiner contends that the breadth of the claims is excessive and that the claims encompass a large number of tumor-associated antigens for which there is not adequate written description support or enablement in the specification. The Examiner also contends that there is no evidence of a prophylactic or therapeutic effect of a vaccine comprising an effective amount of a recombinant influenza virus having a genome containing a region encoding a tumor-associated antigen. These rejections are in error and should be withdrawn for the reasons detailed below.

In the first place, the invention is directed to recombinant influenza viruses having a genome which contains a region encoding a tumor antigen. Applicants are not claiming tumor antigens. Indeed, tumor antigens were well-known in the art as of the filing date of the

application. Rather, the claimed invention is directed to recombinant influenza viruses which have been engineered to encode tumor antigens which have defined structures and functions.

The specification is replete with descriptions of tumor-associated antigens that could be engineered into the genome of recombinant influenza viruses. In this regard, the Examiner's attention is directed to the specification at p. 8-10 and p. 15-17 for written description support for tumor-associated antigens that can be engineered into the genome of recombinant influenza viruses. Moreover, contrary to the Examiner's contention that the tumor antigens listed in Table 1 are not tumor-associated antigens, Applicants assert that the tumor antigens listed in Table 1 would be understood by one of skill in the art to be tumor-associated antigens. In fact the specification at page 7, lines 22-25, refers to the tumor antigens in Table 1 as tumor-associated antigens. However, as noted above, in order to expedite the prosecution of the application, Applicants have amended claims 1, 4, and 20 to recite "tumor antigens" rather than "tumor-associated antigens". Thus, the specification does, indeed, provide adequate written description support of tumor antigens which can be engineered into the genome of recombinant influenza viruses.

Clearly, the structures of tumor antigens (*e.g.*, the polynucleotide sequences of the tumor antigens) that could be used in accordance with the invention were known in the art as of the filing date of the present application. Indeed, many relevant publications regarding tumor antigens/tumor-associated antigens are cited in the text of the specification (see, *e.g.*, p. 2, lines 16-35 and p. 8, Table 1). For example, the structures of human tumor antigens, recognized by T lymphocytes, including their polynucleotide sequences, were well-known in the art as of the filing date of the instant application, and their use in vaccines and immunotherapy was well-documented. Applicants respectfully invite the Examiner's attention to the following references which describe human tumor antigens which recognize T lymphocytes: Osanto S., 1997, *Oncologist*, 2(5):284-99; Durrant LG., 1997, *Anticancer Drugs,* 8(8):727-33; Rosenburg SA. et al., 1998, *J. Natl Cancer Inst.*, 90(24):1894-900; and McCabe BJ. et al., 1995, *Cancer Res.*, 55:1741-7.

In particular, the specific examples of tumor antigens, listed in Table 1 of the instant application, melanocyte lineage proteins (*i.e.* gp100, MART-1/MelanA, TRP-1), MAGE-1, MAGE-3, BAGE, GAGE-1, N-acetylglucosaminyltransferase-V, p15, β-catenin, MUM-1,

CDK4, breast and ovarian tumor antigens (*i.e.* HER-2/neu. MUC-1), cervical carcinoma (*i.e.* human papillomavirus E6 and E7), and pancreatic carcinoma (*i.e.* MUC-1), were well -known to those skilled in the art and were well-characterized as of the filing date of the instant application. For example, the expression patterns and the sequences of MAGE, BAGE, and GAGE gene products were well-known to those skilled in the art as of the filing date of the instant application (see, *e.g.,* GENBANK accession numbers U10340 U03735, U19142, and U19143, for the nucleotide sequences encoding MAGE-1, MAGE-3, GAGE-1 and GAGE-2, respectively). Moreover, those skilled in the art as of the filing date recognized that MAGE, BAGE, and GAGE were appropriate target molecules for the development of cancer vaccines. See, *e.g.*, Itoh et al., 1997, *Int. Rev. Immunology*, 14(2-3):153-71; Maeurer M.J. et al., 1996, *Melanoma Res.*, 6(1):11-24; and Kawakami Y. et al., 1996, *Keio J. Med.*, 45(2):100-8.

Human tumor antigens of melanocyte origin were also well-known to those of skill in the art and were well-characterized as of the filing date of the application. For example, the sequences of MART-1, gp100, and TRP-1 were well-known to those of skill in the art as of the filing date of the application (see, *e.g.*, GENBANK accession numbers of U06452, N28728, and X60955, respectively; and Zhai et al., 1997, *J. Immunother.*, 20(1):15-25; and Kawakami and Rosenburg, 1996, *Immunol. Res.* 15(3):179-90). Additionally, recombinant adenoviruses encoding MART-1 and gp100 have been characterized by others (Zhai et al., 1996, *J. Immunology*, 156(2):700-10).

Further, human breast and ovarian tumor antigens (*i.e.* HER-2/neu, MUC-1), cervical tumor antigens (*i.e.* human papilloma virus E6, E7), and pancreatic tumor antigens (*i.e.* MUC-1) were also well-characterized as of the filing date of the application. As of the filing date of the application, the expression patterns and nucleotide sequences of human breast tumor antigens and ovarian tumor antigens cervical tumor antigens, and pancreatic tumor antigens were well-known to those skilled in the art (see, *e.g.,* GENBANK accession numbers AH002044 and X64085 for MUC-1 and human papilloma virus respectively; for HER-2/neu see Krainer M. et al., 1997, *Oncology*, 54:475-81; for MUC-1 see Akagi J. et al., 1997, *J. of Immunotherapy*, 20(1):38-47). Further, as of the filing date, these tumor antigens were also considered appropriate target molecules for cancer vaccine development

In view of the foregoing, the instant specification coupled with the information well-known in the art as of the filing date of the application provides adequate written description support of tumor antigens. It is well established that the specification need not describe, and should preferably omit what is known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1367, 231 UPSQ 81 (Fed. Cir. 1986); *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F. 2d. 1527, 25 USPQ2d 1241 (Fed. Cir. 1992); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991).

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics, Inc.* 857 F. 2d 778, 8 USPQ 2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d 1367, 1384 (Fed. Cir. 1986).

Applicants respectfully assert that the specification fully describes the claimed recombinant influenza viruses and vaccines, and coupled with the state of the art, as of the filing date of the application, fully enables one of skill in the art to make and use the claimed recombinant influenza viruses and vaccines without having to resort to undue experimentation.

The specification coupled with the state of the art as of the filing date provides sufficient guidance to one of skill in the art regarding tumor antigens which could be used in the recombinant influenza viruses of the claimed inventions. The specification teaches how to engineer recombinant influenza viruses containing a tumor antigen (see, *e.g.,* instant specification at p. 9, paragraphs 1 & 2, lines 7-24). The specification cites to and incorporates by reference U.S. Patent No. 5,166,057 and International Publication No. WO 93/21306, which provide extensive disclosure to enable one skilled in the art to engineer recombinant influenza viruses containing tumor antigens. In particular, the instant specification teaches methods of generating a recombinant influenza virus using reverse genetics techniques (see, *e.g.,* the instant specification at p. 7, line 1 to p. 10, line 29). Furthermore, the specification teaches in detail and by way of example how to engineer a recombinant influenza virus expressing a model tumor antigen (*i.e.*, β-gal; see, *e.g.,* the

instant specification at p. 15, line 20 to p. 19, line 3). Any tumor antigen well-known in the art can be readily substituted for the prototype antigen described in the example in the specification. A skilled artisan armed with the knowledge of the nucleotide sequences of tumor antigens as of the filing date of the application could easily substitute any tumor antigen, in place of the tumor antigen used in the example, and obtain a recombinant influenza virus containing a desired tumor antigen. Thus, one of skill in the art, as of the filing date of the instant application, would have known how to make and use a recombinant influenza virus having a genome which contains a region encoding a tumor antigen.

In addition, the specification fully enables one of skill in the art to make and use vaccines formulations comprising recombinant influenza viruses with genomes containing tumor antigens. The specification describes methods of producing and administering vaccine formulations (see, *e.g.,* p. 10, line 31 to p. 15, line 16 of the specification). Applicants assert that the cytolytic response and reduction in lung metastases obtained by administering the prototype vaccine formulation described in the example in the specification to mice is indicative of the therapeutic response that one would expect in humans, which have been administered a recombinant influenza virus with a genome containing a tumor antigen.

Further, others in post-filing date publications have described the production of recombinant influenza viruses with genomes containing a region encoding a tumor antigen as taught by the instant specification. Applicants invite the Examiner's attention to Strobel et al., 2000, *Human Gene Therapy*, 1:2207-2218 ("Strobel"; Exhibit B) as an example of the successful production of the recombinant influenza viruses provided by the instant application. Strobel describes the production of a recombinant influenza virus with a genome containing the nucleotide sequence encoding MAGE-3, one of the tumor antigens disclosed in the instant specification. According to Strobel, these recombinant influenza viruses infected dendritic cells and the infected dendritic cells expressed MAGE-3. Strobel states that "[t]he features of this influenza vector suggest that it could be developed into a safe vector system useful for application in humans" (see Strobel at page 2215, first full paragraph). Thus, the recombinant influenza viruses described in the instant specification have been successfully generated by others skilled in the art.

In view of the foregoing, the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-mentioned application is respectfully requested. Applicants believe that the invention defined by the claims meets all the requirements for patentability. Withdrawal of all rejections and reconsideration of the claims is respectfully requested.

If the Examiner has any questions or concerns, she is invited to contact the undersigned individual.

Respectfully submitted,

Date March 13, 2002

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